

Research Article

Prevalence of pulmonary artery hypertension (pah) in patients with thalassemia

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Abstract

Background and objective: Lack of regular blood transfusions in patients with intermediate thalassemia leads to a higher probability of pulmonary arterial hypertension (PAH) in comparison with other patients. PAH remain a concern in thalassemia patients. The aim of this study was to find the prevalence of PAH in patients with thalassemia.

Methods: In this Cross-Sectional study, sixty three matched patients were consecutively admitted to hospital and divided to two groups (29 intermediate and 34 major thalassemia patients). Echocardiography, Complete Blood Count (CBC) and ferritin analysis were done for both groups. The mean pulmonary artery systolic pressure (PASP) values ≥ 25 mmHg defined as PAH. Patients with TI were treated by Hydroxyurea and didn't need regular monthly blood transfusions for maintaining their hemoglobin levels above 9.5. Data collected for each group patients and then analyzed by Statistical methods in SPSS.19.

Results: The prevalence of PAH in patients with TI with 12(41.4%) was significantly 2.8 time higher than patients with TM with 5(14.7%).(p=0.018) Variables such as sex, marital status, age, nucleated red blood cells(NRBC),heart failure, ECG change rate were similar between two groups.

Conclusion: PAH in patients with thalassemia intermediate which treated with Hydroxyurea were significantly more than patients with thalassemia major which receiving regular blood transfusions. Therefore, it was recommended that before appearance the symptoms of pulmonary hypertension in the patients with thalassemia intermediate, especially males, regular blood transfusions to be started in these groups.

Introduction

Pulmonary Hypertension (PHT) is a clinical entity which is not uncommon in thalassemic patients. Thalassemia make a heterogeneous group of inherited anemia due to mutations occurred in the genes formulating hemoglobin. Weaker gene mutations are more frequent, while severe gene mutations are rare [1]. There are a lot of patients who, clinically, have more severe symptoms than minor thalassemia, but the severity of their anemia is not SAME AS major which is called thalassemia major [2]. Today, most experts agree that only a group of thalassemic patients with hemoglobin level between 6 - 10 g/dl who have reached puberty can be included in the category of thalassemia intermediate. However, there are some thalassemia intermediate cases with hemoglobin level above 10 g/dl who remain undiagnosed until puberty, but these cases are rare [2].

Talassemia has numerous complications such as pulmonary hypertension which is caused by pulmonary Hemocidrosis, special chest shape, extra medullary hematopoiesis and rise of coagulability status in patients with intermediate [3-6].

Regular blood transfusions in the thalassemia can prevent pulmonary hypertension. It appears that the probability of pulmonary hypertension in thalassemia intermedia is higher than thalassemia major [7]. The aim of this study was to investigate prevalence and risk factors of pulmonary hypertension (PH) in patients with thalassemia under treatment with Hydroxyurea and its related factors.

Methods

Type of study

This cross-sectional study was conducted on 63 thalassemia patients who had referred to the clinic for treating Thalassemia. From all thalassemia patients, 29 patients with thalassemia intermediate (TI) were chosen as group I and 34 patients with thalassemia major (TM) as group II.

In this study, those were chosen as the thalassemia intermediate patients were treated by Hydroxyurea and didn't need regular monthly blood transfusions for maintaining their hemoglobin levels above 9.5. The Mean pulmonary pressure above 25 mmHg was considered as the pulmonary hypertension. In patients of both groups variables such as age, sex and NRBC were matched and the ECG and Echocardiography were done for all patients in two groups. Data collected by a checklist included some variables such as age, sex, marital status, blood transfusions' frequency, the mean of ferritin level over the last year, having pulmonary hypertension, heart failure, Splenectomy and ECG changes.

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Key words: thalassemia, pulmonary hypertension, hydroxyurea, risk factors, blood transfusion

Received: June 14, 2016; **Accepted:** July 06, 2016; **Published:** July 08, 2016

Statistical analysis

The data were analyzed using SPSS version 19 through descriptive and analytical statistical methods. Mean \pm SD and frequency and percent were used to describe data. Independent t-test and chi-square used for compare data between groups. The level of significance was considered $P < 0.05$.

Ethical Considerations

Verbal consent was obtained from patients. The design of study was approved by ethical committee of the University and registered in IRCT.

Results

In this study, 63 patients participated which from them 29(46%) have TI and 34(54%) have TM. Of the TI patients, 11 (37.9%) had ECG changes. Most of patients in TI group (65.5%) had ferritin below 1000. Of TI patients 12(41.4%) and from TM patients 5(14.7%) have PH and the prevalence of PH in patients with thalassemia intermediate is significantly 2.8 time higher than TM patients ($P=0.018$) (Table 1).

It was found that in TI group, of 12 patients with pulmonary hypertension 10 cases (83.3%) were male and 2 (16.7%) were female with ratio 10:2. The average level of hemoglobin in the group with pulmonary hypertension and the group without pulmonary hypertension was 9.1 ± 1.1 , and 9.4 ± 0.8 , respectively, but not statistically significant. The mean NRBC in the group with pulmonary hypertension was 155 ± 71.5 , and in the group without pulmonary hypertension was 89.2 ± 38.9 , which showed no statistically significant difference between two groups. Table 2 of the 12 thalassemia intermediate patients who had pulmonary hypertension, ten (83.3%) had ECG changes and of 5 thalassemia major patients who had pulmonary hypertension, all had ECG changes. However, there was statistically significant difference between the rate of pulmonary hypertension between two groups. Most of the patients with thalassemia intermedia had ferritin below 1000 with 65.5% and Most of patients with major thalassemia have ferritin in range 1000-4000 with 73.5%.

Discussion

The phenotype of thalassemia intermediate stands between thalassemia minor and thalassemia major. The presence of a range of clinical symptoms for thalassemia intermediate shows the specificity of each patient in terms of the treatment that s/he should receive.

Table 1. Comparison between the two studied groups as regard different variables.

Variables	Group	Intermedia (n=29)	Major (n=34)	p-value
Sex[n(%)]				
Male		18(62.1)	21(61.8)	0.6
Female		11(37.9)	13(39.2)	
Marital status				
Married		14(48.3)	17(50)	0.5
Single		15(51.7)	17(50)	
PAH		12(70.6)	5(14.7)	0.018
Age mean \pm SD		17.7 ± 5.5	19.3 ± 7.2	0.3
Hb mean \pm SD		9.3 ± 0.9	8.3 ± 1.2	0.001
NRBC mean \pm SD		116.3 ± 37.1	84.4 ± 43.4	0.58
ECG change rate		11(37.9)	8(23.5)	0.12
Heart failure rate		2(6.9)	3(8.8)	0.6
Ferritin Levels <1000		19(65.5)	3(8.8)	0.001
1000-4000		9(31)	25(73.5)	
>4000		1(3.4)	6(17.6)	

Table 2. Comparison between PAH and non PAH as regard different variables.

Variables	Group	PAH+ (N=17)	PAH-(N=46)	p-value
Sex[n(%)]				
Male		10 (83.3)	29 (63)	0.047
Female		7 (16.7)	22 (37)	
Hb mean \pm SD		9.1 ± 1.1	9.4 ± 0.8	0.24
NRBC mean \pm SD		155 ± 71.5	89.2 ± 38.9	0.46
ECG change rate		15 (88.2)	2 (4.3)	0.001

Despite availability of several therapeutic approaches, lack of a clear and practical guide can lead to serious doubts over treatment [8].

The severity of clinical outcome largely depends on the initial molecular defects. Deposition of α chains in erythroid precursors in the bone marrow can cause damage to cell membranes and premature cell death and ineffective hematopoiesis. Highly ineffective primary hematopoiesis is determinant of anemia. In addition to complications and common symptoms of thalassemia, a series of specific complications can be seen in thalassemia intermediate due to lack of regular blood transfusions and iron chelation, which is rare in thalassemia major, like gallstones, extra medullary hematopoiesis, kidney stones, leg ulcers and increased thrombophilia and pulmonary hypertension and right heart's failure [8].

It seems that the right heart's failure in this group of patients emanates from pulmonary hypertension. The mechanism of pulmonary hypertension in thalassemia intermediate has not been obviously recognized yet. Inasmuch as anemia and iron overload are very uncommon in the patients with thalassemia major who receive sufficient blood transfusions and iron chelation, it appears that these two actions are the basis for pathophysiology in pulmonary hypertension [2-3,8]. Hereupon, taking regular blood transfusions and iron chelation in patients with thalassemia intermediate in early stages where pulmonary hypertension symptoms occur, seems necessary. In this study, we made an effort to draw a comparison between patients with thalassemia major and patients with thalassemia intermediate in terms of pulmonary hypertension and determine the factors associated with pulmonary hypertension in patients with thalassemia intermediate, with the purpose of avoiding pulmonary hypertension by starting early blood transfusions. Currently, treatment with Hydroxyurea is considered as the first rational choice to treat thalassemia intermediate, while blood transfusion and iron chelation are performed only in particular cases determined by the patient's condition. Of the 63 patients studied, 17 patients (27%) had pulmonary hypertension that 12 patients (41.4%) out of this number belonged to thalassemia intermediate group and rest of them, i.e., five patients (14.4%), belonged to thalassemia major group. It was also shown that the rate of PAH in patients with TI was significantly higher than patients with thalassemia major ($P=0.018$). In similar studies undertaken over patients with TI, the pulmonary hypertension has been assessed in range 4.3%-100% and 60% whose outcomes show higher rates of pulmonary hypertension prevalence in TI patients [9-14].

The incidence rate of pulmonary hypertension in patients with thalassemia major who received regular blood transfusions and iron chelation was much less and confirmed the findings of previous studies [4,8,10-13].

Pulmonary hypertension in the male patients with thalassemia intermediate was significantly greater than female patients ($P=0.047$), that suggests early start of regular blood transfusions and examination of pulmonary hypertension in male patients. Although, there wasn't

any significant relationship between the mean of hemoglobin/NRBC's level and developing pulmonary hypertension in patients with thalassemia intermediate. The mean of hemoglobin in the individuals with thalassemia intermediate who had pulmonary hypertension was lower. In this case, it can be recommended that early blood transfusion and Deferoxamine injection to be performed when the hemoglobin level is low and NRBC level is high. There was no significant relationship between pulmonary hypertension in patients with thalassemia intermediate and the mean age of them. This result might indicate that age cannot be good criteria for predicting when pulmonary hypertension may occur and deciding when to start iron chelation, as evidence, pulmonary hypertension has been observed in the individuals with lower ages. There was significant relationship between ECG changes and pulmonary hypertension in patients with thalassemia intermediate ($P=0.001$), indicating that ECG changes beside changes induced by pulmonary hypertension can be helpful in predicting pulmonary hypertension. There was no significant relationship between the mean of ferritin level and pulmonary hypertension in patients with thalassemia intermediate ($P=0.233$). Thus we could say that the ferritin level cannot be good criteria to predict the incidence of pulmonary hypertension in patients with TI.

Conclusion

Pulmonary hypertension in patients with thalassemia intermediate who are treated with Hydroxyurea instead of regular blood transfusions and iron chelation therapy is significantly higher than in patients with thalassemia major. Therefore, it is recommended that patients with thalassemia intermediate to be regularly examined in terms of the incidence of pulmonary hypertension through performing echocardiography and to begin regular blood transfusions and iron chelation as soon as the symptoms of pulmonary hypertension appear, especially in males and in patients with low hemoglobin and high NRBC.

Furthermore, because of the increasing number of platelets in patients with thalassemia intermediate and its association with pulmonary hypertension, it is suggested that future studies to be conducted in larger groups and the number of platelet to be counted and its association with pulmonary hypertension to be investigated.

Acknowledgement

The authors wish to thank all patients who participated in this study and their families.

Sources of funding

This study was financially supported by research unit in Ardabil

University of Medical Sciences.

Conflict of interest

None.

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